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09/692,807	10/20/2000	Ghazwan Saleem Butrous	PC10370A	6255

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EXAMINER	
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1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/692,807	GHAZWAN SALEMM BUTROUS ET AL.	
	Examiner	Art Unit	
	Dwayne C Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *the amendment of 10 FEB 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-10 and 21-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-10 and 21-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Claims

1. Claims 1 and 7-10 and 21-112 are pending.

2. Claims 1 and 7-10 and 21-112 are rejected.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 7-10, 21, 27, 44, 63-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of pulmonary hypertension with the PDE5 inhibitor of sildenafil, does not reasonably provide enablement for the prevention of pulmonary hypertension with the PDE5 inhibitor of sildenafil. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples;

and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to the prevention of pulmonary hypertension with the PDE5 inhibitor of sildenafil. The method comprises administering the PDE5 inhibitor of sildenafil for the prevention of pulmonary hypertension.

(2) The state of the prior art

The compound of the invention is the PDE5 inhibitor of sildenafil. However, the prior art reference of Ellis et al. of WO 94/28902 teach of a variety of treatments for the compound of sildenafil and its derivatives, but Ellis et al. do not teach of the prevention of pulmonary hypertension with sildenafil.

(3) The relative skill of those in the art

The relative skill of those in the art of is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often

react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art0; In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of the PDE5 inhibitor of sildenafil and its derivatives prior to filing of the instant invention was an unpredictable art.

(5) The breadth of the claims

The instant claims are very broad. For instance, claim 1 is directed to the PDE5 inhibitors, namely sildenafil. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.),cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded

amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of a PDE5 inhibitor of sildenafil to be effective in preventing pulmonary hypertension is insufficient for enablement. The specification provides no guidance, in the way of enablement for the prevention of pulmonary hypertension with PDE5 inhibitor of sildenafil other than the prevention of

pulmonary hypertension with PDE5 inhibitor of sildenafil. In addition, the specification does not provide any enablement the prevention of pulmonary hypertension with PDE5 inhibitor of sildenafil. See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

(7) The presence or absence of working examples

As stated above, the specification discloses the treatment of pulmonary hypertension with PDE5 inhibitor of sildenafil. However, the instant specification only has enablement for the treatment of pulmonary hypertension with PDE5 inhibitor of sildenafil.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the how the PDE5

inhibitor of sildenafil is used for the prevention of pulmonary hypertension when the instant specification only provides enablement for the treatment of pulmonary hypertension with the PDE5 inhibitor of sildenafil.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 7, and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There valence number of two carbon atoms is exceeded at the two bridgeheads in compound of formula d). this ambiguity renders the claim vague and indefinite.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Takahashi et al., which has a publication date of 19961997 for the instantly claimed compound entitled d) of claim 1. Takahashi et al. teach of the administration of E4021, which is a type V phosphodiesterase inhibitor. Takahashi et al. are directed to the administration of a type V phosphodiesterase inhibitor to protect against the

development of right ventricular overload and medial thickening of pulmonary arteries in order to treat pulmonary hypertension.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1 and 7-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902 possessing a publication date of December 22, 1994, especially for sildenafil and its derivatives. Ellis et al. teach of compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). This selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The skilled artisan would have been motivated to treat patients with pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan that these inhibitors of cGMP PDE are used to treat both hypertension and pulmonary hypertension. Ellis et al. specifically teach of inhibitors of cGMP PDEs with the compounds of formula (I). In fact, Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when R^1 is methyl; R^2 is n-propyl; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). Ellis et al. also teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). Ellis et al. teach of various modes of administration for these compounds, inter alia, oral and parenteral administration, (see page 10). Ellis et al. further teach of a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The determination of a dosage having the optimum therapeutic index, modes and methods of administration,

for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. Accordingly, the Ellis et al. reference renders the instantly claimed invention obvious.

13. Claims 1, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902, which has a publication date of December 22, 1994, for the instantly claimed compounds entitled c) and e) and f) of claim 1. Ellis et al. teach of compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). This selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). Ellis et al. specifically teach of inhibitors of cGMP PDEs with the compounds of formula (I). In fact, Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when R^1 is methyl; R^2 is n-propyl; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). The compounds disclosed by Ellis et al. have a structurally similar core structure with the a 1,3-diaziny –4 –keto moiety and other identical substituents on position no. 2 of the 1,3-diaznyl ring moiety. Furthermore, the physiological activities are analogous. The claims differ from the prior art by having an imidazole moiety and an indole moiety, respectively instead of the pyrazole moiety of Ellis et al. Also, Ellis et al. teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). Ellis et

al. teach of various modes of administration for these compounds, inter alia, oral and parenteral administration, (see page 10). Ellis et al. further teach of a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. In addition, one having ordinary skill in the art would have been motivated to select the claimed compound with the expectation that substitution of a heterocyclic ring moiety, such as imidazole or indole moieties, for another, namely a pyrazole moiety, would not significantly alter the analogous properties of the compound of the reference due to the close structural similarity of the compounds. For these reasons the instantly claimed compounds entitled c) and e) and f) of claim 1 are rendered obvious over Ellis et al.

14. Claims 1, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kato et al. of JP 09059159 A2, which has an issue date of March 4, 1997 for the instantly claimed compound entitled d) of claim 1. Kato et al. teach of 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium salt. Kato et al. also teach that these compounds are useful for the treatment of pulmonary hypertension, (see abstract). In addition, the determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary

skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. It would have been obvious to one having ordinary skill in the art to employ the compound of Kato et al. even though Kato et al. is silent to the functional activity of PDE5 inhibitory activity of this compound. As a result, the instant invention is rendered obvious in view of Kato et al. since the determination of dosage and methods of using is well within the purview of the skilled artisan.

15. Claims 1, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al., which has a publication date of 19961997 for the instantly claimed compound entitled d) of claim 1. Takahashi et al. teach of the administration of E4021, which is a type V phosphodiesterase inhibitor. Takahashi et al. are directed to the administration of a type V phosphodiesterase inhibitor to protect against the development of right ventricular overload and medial thickening of pulmonary arteries in order to treat pulmonary hypertension. Moreover, the determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (703) 308-4634. The examiner can normally be reached on Mondays through Fridays from 8:30 am to 6:00 pm. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

DWAYNE C. JONES
PRIMARY EXAMINER

Tech. Ctr. 1614
June 23, 2003